REMARKS

Claims 1-4, 7, and 8 are pending in the present application.

Claims 5 and 6 were previously canceled without prejudice or disclaimer.

Claims 1-4, 7, and 8 have been amended. Claims 1-4 have been amended to recite "consisting essentially of," which replaces the "comprising" transitional phrase. Claims 7 and 8 have been amended to be consistent with amendment of Claim 1.

No new matter has been added. Reconsideration and allowance are respectfully requested in view of the following remarks.

Applicants' representative thank Examiner Kantamneni and Supervisor, Sreeni Padmanabhan for granting an interview on August 28, 2007.

Rejections Under 35 U.S.C. § 103(a)

MPEP §2143 provides that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure." (MPEP sec. 2143 quoting *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

I

Claims 1-4, and 8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Keller et al.* ("*Keller*") (WO 9834595, English equivalent to US 6,461,591, PTO-892 of record), in view of *Palmer Douglas* ("*Palmer Douglas*") (EP 0416950, PTO-892). It is alleged that *Palmer Douglas's* process for making dry powder formulation comprising classical corticosteroids and beta-mimetics can be utilized for producing the claimed powdered pharmaceutical composition comprising loteprednol or loteprednol etabonate ("soft steroid" and not classical corticosteroids) and at least one β_2 adrenoreceptor agonist.

Applicants traverse and submit that a *prima facie* case of obviousness has not been established. Applicants assert that *Keller* and *Palmer Douglas* do not suggest the combination of the elements recited in independent Claim 1.

Claim 1, as amended, recites: A powdered pharmaceutical composition, consisting essentially of:

formulated separately or together,

an efficacious amount of (i) loteprednol or loteprednol etabonate; and (ii) at least one β_2 adrenoreceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,

for administration by inhalation, wherein the pharmaceutical composition is formulated in a powdered form.

In the formulation recited in Claim 1, the (i) loteprednol functions as anti-inflammatory agent, and the (ii) β_2 adrenoreceptor agonist functions as a bronchial dilator.

As pointed out in the Reply filed February 13, 2007, *Keller* does not disclose the claimed pharmaceutical composition comprising a combination of (i) loteprednol or loteprednol etabonate and (ii) β_2 adrenoreceptor agonists, as recited in Claim 1. *Keller* merely provides a list of pharmaceutically active compounds that may be included in their aerosol formulations (see Col. 7 of *Keller*). Again, Applicants point out that *Keller* does not specifically disclose this particular combination of agents recited in Claim 1: (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists. Applicants note that none of Keller's exemplary formulations include this particular combination of a soft steroid with a β_2 adrenoreceptor agonist, as recited in Claim 1. Applicants have amended Claims 1-4 to substitute the "comprising" transitional phrase with the phrase "consisting essentially of," to further distinguish the claimed formulation.

In addition, Applicants provide unexpected results within the specification, which were noted in the previously filed Reply (2/13/2007), and presented again (below) for the convenience of the Examiner:

Technical Distinctions, Synergistic Results, and Comparative Tests

Applicants are submitting two technical documents with this Amendment in order to point out that the compounds referred to as "loteprednol" and "corticoids" (classic steroids) can be structurally and functionally different. Loteprednol etabonate is structurally distinguishable from other corticosteroids in that the ketone group at number 20 position is not present in loteprednol etabonate that confers high lipid-solubility for enhancing penetration into cells (See attached "Physicians' Desk Reference: OPT - Alrex Ophthalmic Suspension 0.2% (Bausch & Lomb), at page 2 of 7). The low toxicity of loteprednol etabonate is attributed to the formation of inactive metabolites within the bodies of patients. In addition, Applicants have attached an excerpt from Drugdex Evaluations in order to show that Loteprednol ("soft steroids") is distinguishable from the classical steroids having a different mechanism of action that leads to greater toxicity effects (see page 11 of 17).

Applicants note that at the time of the present invention, loteprednol was appreciated mainly for opthalmic clinical applications, and the possibility of utilizing loteprednol etabonate in combination with beta-mimetics for the treatment of asthma bronchiale had not been appreciated. Furthermore, the synergistic effect of the combination of loteprednol etabonate and beta-mimetics (as shown in Tables 1 and 2) was unexpected.

Furthermore, Applicants have distinguished the properties of soft corticosteroids (from that of classical corticosteroids) in the Specification by explaining that soft corticosteroids, such as loteprednols or loteprednol etabonates, are more readily metabolized (inactivated) *in vivo* by engaging a different metabolic pathway compared to classical corticosteroids, such as beclomethasone dipropionate (BDP) or budesonide (BUD), which are known to have relatively higher *in vivo* stability resulting in many deleterious side effects experienced by patients (see lines 21-31, at page 2 of the Specification). Applicants have further explained differences in the side effects produced by classical corticosteroids and soft corticosteroids to distinguish the claimed compositions and methods from the prior art (see lines 10-30, page 7 of the Specification). The claimed combination is especially beneficial for children who are especially sensitive to the deleterious side effects caused by classical corticosteroids, which includes growth retardation, osteoporosis, and an increase in intraocular pressure.

Furthermore, Applicants submit that the Office has not fully appreciated the experiments performed by the Applicants, as shown in the Specification. These experiments provide unexpected advantages, resulting from the co-administration of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor agonists. The specification provides data showing synergistic effect caused by the co-exposure to a mixture of (1) loteprednol or loteprednol etabonate; and (2) β_2 adrenoceptor agonists, under *in vitro* and *in vivo* conditions. The specification provides **comparative data** showing a less deleterious effect by loteprednol in comparison to classical corticosteroids. The specification also provides comparative data showing enhanced therapeutic effect by loteprednol in comparison to classical corticosteroids.

Table 1 of the specification shows *in vitro* synergistic (over-additive) effect (44%) of the mixture of loteprednol and salbutamol on blood cells as measured by the level of inhibition on TNF-alpha release, compared to samples exposed only to either loteprednol (1%) or salbutamol (17%) alone (see page 5 of the Specification).

Table 2 shows *in vivo* synergistic effect (36 - 65%) of a mixture of loteprednol and formoterol on guinea pigs as measured by the level of inhibition of eosinophilia, compared to samples exposed only to either loteprednol (11-22%) or formoterol (4-20%) alone (see page 6 of the Specification).

Table 3 shows gross reduction in thymus mass in rats exposed to classical corticosteroids, including fluticasone (65%), beclomethasone (51%), and budesonide (89%), in comparison to loteprednol (15-28%). This suggests that the co-administration of loteprednol in combination with β_2 adrenoceptor agonists would likely produce the over-additive effect exemplified in Tables 1 and 2 in patients, while providing advantages for avoiding some of the deleterious side effects associated with classical corticosteroids that have been well-documented in the prior art, including the cited references (see page 8 of the Specification).

Table 4 shows enhanced therapeutic breadth after long-term exposure to loteprednol (45.5) in comparison to modest or low therapeutic efficacy observed for classical steroids, such as fluticasone (33) and budesonide (5) (see page 10 of the Specification).

Because Keller discloses only pressure-liquefied propellant mixtures for the preparation of aerosols formulated for administration by using pressurized inhalants (see Table 1, Col. 12 of *Keller* and Examples 1-14, Cols. 11-14 of *Keller*) and does NOT disclose powdered formulations, as recited in Claims 1-4, the Examiner cites *Palmer Douglas* as providing this claim element. However, Applicants assert that *Palmer Douglas* does not remedy the deficiencies of *Keller*. Under the MPEP §2143, a *prima facie* case of obviousness is established when **three basic criteria have been satisfied**: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all claim limitations. Applicants submit that pharmaceutical agents such as (i) loteprednol or loteprednol etabonate; and (ii) β_2 adrenoreceptor agonists are compounds that have unpredictable properties, individually, and that the efficacy of the combination of (i) loteprednol or loteprednol etabonate; and (ii) β_2 adrenoreceptor agonists is also unpredictable from their respective structures. Thus, Applicants assert that neither references suggest the combination of the elements recited in Claim 1 (point (1)), and that the possibility of achieving success for this particular combination recited in Claim 1 is not reasonably expected (point (2)). Because a *prima facie case* for obviousness has not been established, and in view of the

unexpected results, Applicants respectfully request the withdrawal of the rejection of Claims 1-4, 7 and 8 under 35 U.S.C. §103(a).

II

Claim 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Keller et al. in view of Doi, Koji (WO 9831343 of record) and Bjerkec (of record) and van der Molen (of record).Claim 7 stands rejected under 35 U.S.C. §103(a) in view of *Keller et al.* ("*Keller*") and *Doi et al.* ("*Doi*") (WO 98/31343), *Bjermer et al.* ("*Bjermer*"), and *van der Molen et al. ("Molen").*

Applicants traverse and submit that a *prima facie* case of obviousness has not been established. Applicants assert that none of the cited references suggest the combination of steps of the method recited in Claim 7. *Keller* does not disclose a method for treating asthma bronchiale by co-administrating the combination of (i) loteprednol or (loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents, as recited in Claim 7. In previous Official Actions, the Examiner acknowledged that "Keller does not expressly disclose the employment of the inhalable medicinal aerosol composition comprising the combination as instantly claimed ...," and which is acknowledged again in the present Official Action.

Furthermore, *Bjermer, Doi,* and *Molen*, do not disclose/suggest the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents **for treating asthma bronchiale**, as recited in Claim 7. If none of the cited references discloses or suggests the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents

for treating asthma bronchiale, as recited in Claim 7, then who is combining these elements? Applicants have combined the elements of Claim 7 and have experimentally tested such combinations. The Examiner bases the rejection of Claim 7, on a mere allegation of "reasonable expectation of treating asthma" without establishing that at least one of the cited references provides the requisite suggestion or motivation to combine the elements of Claim 7, or establishing that the success for combining the elements of Claim 7 is reasonably expected.

Furthermore, the Examiner cites *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980, for holding that combining "two compositions, each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art" is deemed to be prima facie obvious. Applicants point out that the relevant facts have been stretched in favor of the Examiner's conclusion of the obviousness of the method of Claim 7. Of all cited references, only *Doi* describes a composition comprising loteprednol in particular, and *Doi's* composition is formulated for use as a nasal suspension, and the possibility of using the composition for the treatment of any type of asthma, let alone asthma bronchiale, in not mentioned. The Examiner states that "Doi discloses that loteprednol etabonate is known to be useful in a pharmaceutical composition and a method of treating inflammatory conditions or allergy since loteprednol etabonate has excellent anti inflammatory conditions or antiallergic activities and is value as a drug in an ointment or a liquid form, and loteprednol etabonate is formuated into a long-term stable liquid suspension for nasal administration". Based on this, the Examiner alleges that "one of ordinary skill in the art could have been motivated to employ

loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a method for the treatment of allergies and/or airway disorders such as asthma bronchiale" (emphasis added). If *Doi* is the only cited reference that discloses the use of loteprednol etabonate, and if *Doi* does not describe the use of the loteprednol etabonate-containing nasal drips for the treatment of "airway disorders such as asthma bronchiale," then how is the holding of *In re Kerkhoven* relevant here, when the purpose of *Doi* (anti-allergic agent) is not the same purpose as the method of Claim 7 (treatment of asthma bronchiale)? Applicants submit that absent a teaching from the cited references to combine (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor, a *prima facie case* for obviousness has not been established. Thus, Applicants respectfully request the withdrawal of the rejection of Claim 7.

CONCLUSION

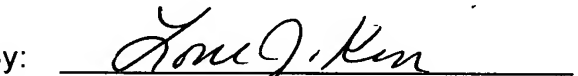
From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of present application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 30, 2007

By: 
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